REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 44, 46, 52-57, 59-60 and 63-74 will be pending in the application. Claims 45, 50, 58, 61 and 62 are cancelled herein without prejudice. Applicants reserve the right to pursue the subject matter of these claims in one or more continuing applications. Claims 44 has been amended to correct clerical errors and incorporate cancelled claim 45. Claim 46 has been amended to correct clerical errors. Claims 63 and 74 have been added. Support for claims 63 and 74 can be found in claim 43 as originally filed. Claims 64-73 have been added to depend from new claim 63. Support for claim 64 can be found at page 24, lines 20-25, support for claim 65 can be found at page 21, lines 13-16 and support for claims 66-73 can be found in pending claims 52-57 and 59-60. No new matter is added by these amendments.

Applicants thank the Examiner for the courtesy extended during the telephonic discussion on June 24, 2005. Applicants appreciate the opportunity to discuss the issues in the application.

Applicants are concurrently submitting an Information Disclosure Statement, including the references cited herein, for consideration by the Examiner.

In support of the remarks and arguments stated *infra*, Applicants have submitted herewith the Declaration of Dr. Ronit Sagi-Eisenberg under 37 C.F.R. §1.132.

REJECTIONS

Rejections under 35 U.S.C. 103

Claims 44-46 and 52-60 stand rejected under 35 U.S.C §103 as being unpatentable over Kuby et al. (herein referred to as "Kuby") in view of Aridor et al. (herein referred to as "Aridor") and U.S. Pat. No. 5,807,746 to Lin (hereafter referred to as "Lin").

With respect to Kuby, the Examiner states that Kuby discloses that the inhibition of mast cell degranulation is a known mechanism to treat allergies (*See*, Office Action at page 3). With respect to Aridor, the Examiner states that Aridor teaches the use of two peptides KNNLKECGLY and KENLKDCGLF in inhibiting mast cell degranulation when given to permeabilized cells, *in vitro*. Finally, with respect to Lin, the Examiner states that Lin teaches adding the sequence AAVALLPAVLLALLAP to any known biologically active peptide to

allow transportation of the active peptide to the inside of the cell to allow for *in vivo* therapies (*See*, Office Action at page 3).

The Examiner states that one of ordinary skill in the art would be motivated to add the importation peptides of Lin to the peptides taught by Aridor to treat allergies as treating allergies with mast cell degranulator inhibitors was well known in the art as taught by Kuby and that one of ordinary skill in the art would have a reasonable expectation of success in producing the claimed invention (*See*, Office Action at page 3).

Applicants traverse the rejection as applied to pending claims 44, 46, 52-57, 59-60 and 63-74, as amended and added herein and submit that one of ordinary skill in the art would have no reasonable expectation of success combining the teachings of Kuby, Aridor and Lin to reach the presently claimed method for treating an allergic condition in a subject *in vivo* by administering the complex molecule of SEQ ID NO:12 or SEQ ID NO:7.

A proper obviousness analysis (*See*, MPEP § 2143) requires consideration of "whether the prior art would also have revealed that in so making or carrying out [the claimed invention], those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d at 493. Further, "(t)he consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988).

Aridor teaches the use of the two peptides KNNLKECGLY and KENLKDCGLF in inhibiting mast cell degranulation when given to permeabilized cells, *in vitro*.

Lin broadly teaches that any biological active molecule (*See*, Lin column 3, line 40 - column 4, line 8) can be linked to any importation signal peptide (*See*, Lin column 6, line 20 - column 7, line 17; column 8, lines 35-44) to import the biological active molecule into any cell (*See*, Lin column 8, lines 24-35), *in vitro*, *ex vivo* or *in vivo* (*See*, Lin column 5 lines 7-44).

Following the teachings of Aridor and Lin and the Examiner's reasoning, one of ordinary skill in the art would have a reasonable expectation of success combining any importation signal peptide, to import any biological active molecule, into any cell, *in vitro*, *ex vivo* or *in vivo*; and more specifically, if that biological active molecule is KNNLKECGLY and KENLKDCGLF, the skilled artisan would have a reasonable expectation of success in treating an allergic condition in a subject, *in vivo*. Applicants respectfully disagree for the reasons discussed *infra*.

The claimed invention has two requirements: a) that the complex molecule (comprising an importation competent segment linked to an anti-allergic segment) be able to enter the cell *in vivo* and b) the complex molecule must be biologically active within the cell *in vivo* to exert its anti-allergic effect, thereby treating an allergic condition in a subject. *See*, Eisenberg Declaration ¶ 7.

Specifically, Lin and the instant specification show that the skilled artisan would not have a reasonable expectation of success in linking any importation signal peptide with any biological active molecule to allow the biological active molecule to be imported into a cell *in vivo* and be biologically active to exert its therapeutic effect within the cell, *in vivo*. (Emphasis Added). *See*, Eisenberg Declaration ¶ 8.

Lin discloses that, when compared to aFGF not linked to the importation peptide (k-FGF), the importation peptide kFGF linked to aFGF is less mitogenicically potent as shown by thymidine incorporation and DNA synthesis assays (*See*, Lin column 15, line 59 – column 16, line15; Figure 1; Table 2). In fact, the decreased mitogenic potency is significant, as aFGF not linked to an importation peptide at a concentration of 15 ng/ml stimulates DNA synthesis at a level more than twice that of the importation peptide comprising aFGF at 100 ug/ml (a concentration 10,000 fold greater than the concentration of aFGF) (*See*, Lin column 15, line 59 – column 16, line15; Figure 1; Table 2). *See*, Eisenberg Declaration ¶ 8.

Moreover, the description in the present invention further demonstrates the unpredictability of linking any importation competent signal peptide with either KNNLKECGLY and KENLKDCGLF to import the complex molecule into a cell, *in vivo*, such that the complex molecule retains its biological activity to exert its anti-allergic effect within the cell, *in vivo*. Specifically, Applicants synthesized six peptides comprising one of three importation competent signal peptides VTVLALGALAGVGVG (Human Integrin β_3 signal sequence), AAVALLPAVLLALLAP (Kaposi FGF signal sequence) and RQPKIWFPNRRKPWKK (*Antennapedia*, Drosophila transcription factor homeodomain signal sequence) linked to either KNNLKECGLY (C-terminus of $G\alpha_i$) or KENLKDCGLF (C-terminus of $G\alpha_t$) (*See*, page 13, lines 7-18). Based on the teachings of Aridor and Lin, as well as the Examiner's assertions, a skilled artisan would reasonably expect all six polypeptides to be imported into a mast cell *in vivo* and remain biologically active to exert its anti-allergic effect in the cell *in vivo* to treat an allergic condition in the subject. *See*, Eisenberg Declaration ¶ 9.

However, as is shown by the present invention, the biological activity (*i.e.*, anti-allergic effect) of these six peptides is highly divergent and unpredictable *in vitro* or *in vivo*. Specifically, the peptide VTVLALGALAGVGVGKNNLKECGLY (peptide 1, SEQ ID NO:6), comprising the leader motif of the signal sequence within human integrin β3 fused to Gαi3 C-terminal sequence was unable to exert an anti-allergic effect *in vitro* or *in vivo* as it failed to display any inhibitory activity (*See*, page 18, line 19 - page 19, line 3; Figure 3). Whereas, the peptide RQPKIWFPNRRKPWKKKNNLKECGLY (peptide 3, SEQ ID NO:10), which comprises the leader motif of Antennapedia, the Drosophila transcription factor fused to Gαi3 C-terminal sequence not only was unable to exert an anti-allergic effect *in vitro* or *in vivo*, this peptide induced histamine secretion (Emphasis Added) (*See*, page 17, lines 2-4; Figure 1C). Thus of the six peptides synthesized in the present invention, only two of these six peptides: AAVALLPAVLLALLAPKENLKDCGLF (peptide 5, SEQ ID NO:12) and AAVALLPAVLLALLAPKNNLKECGLY (peptide 2, SEQ ID NO:7), were able to exert their anti-allergic effect in a cell *in vitro* or *in vivo* to treat an allergic condition in the subject. *See*, Eisenberg Declaration ¶ 10.

The results of the present invention readily demonstrate that fusing a mast cell degranulation peptide as disclosed in Aridor to an importation sequence peptide as disclosed in Lin does not predictable result in a peptide which can be imported into a mast cell *in vivo* and remain biologically active to exert its anti-allergic effect in the cell *in vivo* to treat an allergic condition in the subject as claimed by the present invention. *See*, Eisenberg Declaration ¶ 11.

For the foregoing reasons, Applicants submit that one of ordinary skill in the art would have no reasonable expectation of success combining the teachings of Kuby, Aridor and Lin to reach the presently claimed invention and request withdrawal of the present rejection.

Rejections under 35 U.S.C. 112, First Paragraph

Claim 44 and 52-62 are rejected under 35 U.S.C. §112, first paragraph, because the specification does not reasonably provide enablement for the use of any importation molecule to treat allergies. Claims 58 and 61-62 are cancelled herein. Applicants traverse the rejection as applied to pending claims 44, 46, 52-57, 59-60 and 63-73, as amended and added herein.

Applicants have amended claim 44 from which claims 46, 52-57 and 59-60 properly depend to recite that the complex molecule is a peptide having an amino acid sequence AAVALLPAVLLALLAPKENLKDCGLF (SEQ ID NO:12) and have added claim 63 from which claims 64-73 properly depend to recite that the complex molecule is a peptide having an

amino acid sequence AAVALLPAVLLALLAPKNNLKECGLY (SEQ ID NO:7). Applicants submit that the specification, specifically page 13, lines 7-23 and Examples 1-4 on pages 14-35 enables one of ordinary skill in the art to make and use the invention commensurate with the scope of the claims as amended and added herein. Applicants request withdrawal of the present rejection.

Further, the Examiner rejects claim 52 for reciting multiple sclerosis (MS) as an allergic condition to be treated by the claimed complex molecules. Specifically, the Examiner alleges that mast cell degranulation is not recognized to be involved in causing pathology of MS, and therefore, since there is no working example demonstrating the use of the peptides of the invention in treating MS, such use cannot be claimed. Applicants respectfully traverse.

Growing evidence suggests that mast cells (MCs) play a crucial role in the inflammatory process and the subsequent demyelination observed in patients suffering from MS. Zappulla J.P. et al. (J Neuroimmunol. 2002. 131(1-2):5-20) stated that "Although no consensus exists on the role of mast cells in multiple sclerosis, recent results from animal models clearly indicate that these cells act at multiple levels to influence both the induction and the severity of disease. In addition to changing our views on the pathophysiology of multiple sclerosis, the concept that mast cells are critical for the outcome of the disease could have an important impact on the development of new therapeutic approaches." *See*, Eisenberg Declaration ¶ 13.

A recent review of Behi M.E. et al. (Immunol Lett. 2005. 15:96(1):11-26) shows number of evidences for the involvement of mast cells in MS. In central nervous system (CNS) of MS patients, increased mast cell population and activity have been documented. Ibrahim et al. (J. Neuroimmunol. 1996. 70:131–138) have identified variable numbers of MCs both inside and around MS plaques. Moreover, the number of MCs around plaques was lower in acute lesions than in chronic active plaques, suggesting that the presence of MCs appears as a consequence of inflammation. Recently, the distribution of MCs in the brains of four MS patients showed that no MCs could be observed in healthy brains, while some MCs were present in MS plaques, essentially clustered around venules and capillaries. Another link between MCs and MS pathology is suggested by findings showing high concentrations of MC-released mediators, such as histamine and tryptase, an MC specific protease, in the cerebrospinal fluid of MS patients (Rozniecki J.J. et al. 1995. Ann Neurol. 37(1):63-66. Several potential roles have been proposed for allergy mediators released by MCs in experimental autoimmune encephalomyelitis (EAE) and MS disease. One of these is the role

of MC mediators in the breakdown of the blood brain barrier (BBB), an early and key event in the development of disease, opening the way to extravasation of inflammatory cells and molecules into the brain. As such, it has been shown that local alterations of BBB permeability after injection of the MC degranulator compound 48/80 (C40/80) into experimental models have been occurred. MCs can also directly participate in the destruction of myelin in MS and EAE. MCs were shown to degranulate in response to major basic protein (MBP), leading to *in vitro* demyelination, and this process was essentially mediated by secreted proteases. *See*, Eisenberg Declaration ¶ 14.

These findings, many available at the time of filing of the instant application, and the description of the role of substance-P induced neurogenic inflammation described in the specification at page 3, lines 11-18 highlight the importance of the role of MCs in MS. As such, one of ordinary skill the art would readily recognize that the modulation of mast cell functions using the complex molecules of the present can provide a novel therapeutic tool for the control of this human demyelinating disease and therefore, the specification and the state of the art at the time of filing, enables one of ordinary skill in the art to make and use the invention as claimed to treat multiple sclerosis. *See*, Eisenberg Declaration ¶ 15.

Rejections under 35 U.S.C. 112, Second Paragraph

Claim 44, 50 and 52-60 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claims 50 and 58 are cancelled herein. Applicants have amended claims 44 and 46, from which the remaining claims subject to the rejection depend, to recite the term "complex molecule" uniformly throughout. Applicants submit this rejection is now moot and should be withdrawn.

CONCLUSION

In view of the aforementioned remarks and amendments, the Applicants believe that each of pending claims is in condition for allowance. Reconsideration, withdrawal of the rejections, and passage of the case to issue is respectfully requested. A notice to this effect is earnestly solicited.

If, upon receipt and review of this amendment, the Examiner believes that the present application is not in condition for allowance and that changes can be suggested which would place the claims in allowable form, the Examiner is respectfully requested to call Applicant's undersigned counsel at the number provided below.

Respectfully submitted,

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Dated: August 24, 2005

TRA 2057920v1